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(54) **Stable parenteral solution of 2-phenyl-1.2-benzisoselenazol-3(2H)-one and process for producing the same.**

(57) The present invention is related to new parenteral preparations of 2-phenyl-1.2-benzisoselenazol- 3(2H)-one (Ebselen) comprising additionally one or several phospholipids and, possibly, one or several auxiliary agents. The invention is further related to a process for producing such solutions and their use in the preparation of drug preparations of Ebselen.

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**Stabile parenteral solution of 2-phenyl-1,2-benzisoselenazol-3(H)-one and process for producing the same**

The present invention is related to new solutions which may be parenterally administered and which comprise 2-phenyl 1,2-benzisoselenazol-3(2H)-one (Ebselen) in combination with one or several phospholipids in a weight proportion of from 1:2500 to 1:15 and, possibly, one or several auxiliary agents. The invention is further related to the production of such solutions as well as their use in the production of drug preparations comprising 2-phenyl-1,2-benzisoselenazol-3(2H)-one (Ebselen) and one or several phospholipids.

Ebselen is a known product (DE-PS 3027073). It may be produced by the process of R. Weber and M. Renson, Bulletin de la Soc. Chim. de France 1976 (7/8), pgs. 1124-1126, by subjecting 2-methylseleno-N-phenyl-benzamide to reaction with phosphorous pentachloride and subsequently hydrolysing the obtained product. Preparations comprising Ebselen may be used in the treatment of numerous diseases such as the prophylaxis and therapy of infection diseases, the therapy of malignant tumors (DE-OS 3638124), for stimulating the immune system or for the treatment of selen deficiency diseases. Further attention is drawn to the application of the anti-atherosclerotic and anti-inflammatory properties of Ebselen and their application in the therapy of rheumatic diseases (DE-OS 3027073). Ebselen is furthermore an important agent useful in the therapy of deficiencies caused by oxidative stress (DE-OS 3616920) such as liver deficiencies, cardiac infarction, psoriasis and diseases caused by radiation. There is known also a drug preparation for the topical use of Ebselen (DE-OS 3620674), which may be used in the external treatment of inflammatory and allergic skin diseases such as psoriasis.

The broad spectrum of properties is in contrast to a very low solubility of Ebselen in water. Due thereto the use of Ebselen in the form of parenteral solutions is prevented. Preparations comprising organic solvents containing Ebselen dissolved therein do not provide satisfactory results because diluting such solutions with water for injections or with physiological saline solutions cause precipitation of crystals of Ebselen.

It has now been found that surprisingly stable aqueous solutions of 2-phenyl-1,2-benzisoselenazol-3(2H)-one (Ebselen) having a physiological pH may be produced by combining Ebselen with one or several natural or synthetic phospholipids and this in a weight proportion of Ebselen to phospholipid amounting to a ratio ranging from 1:2500 to 1:15. Possibly, further auxiliary agents may be added.

In this way, new aqueous solutions of Ebselen in combination with one or several phospholipids are formed. Such solutions are very suitable for parenteral administration (for instance for intramuscular or intravenous administration) and such solutions show a long existing effectiveness.

For producing such solutions, the components thereof are added to each other and stirred to produce homogeneous solutions in usual manners, for instance by aid of high pressure homogenators. In some instances it is possible to obtain the solutions by simple stirring. Another possibility to produce the solutions is treatment with ultrasonics or by using the so called "French Press".

Products to produce isotonic solutions may be added before or after the preparation of the homogeneous solutions. Such products are sodium chloride, glucose or the like. It may be advantageous to add a base, for instance soda lye or a buffer agent in order to produce a pH close to the physiological pH. The solutions thus prepared may be sterilized in usual manners and filled into ampoules as usual.

In view of the sensitivity of the phospholipids against light and oxygen, it may be preferable to work with the exclusion of oxygen and in a protective atmosphere, and with the exclusion of light.

Both natural and synthetic phospholipids may be used. Natural phospholipids (of plant or animal origin) are in particular phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl inositol, phosphatidyl glycol, cardiolipine or plasmalogenes, which products may be recovered from soybeans or from eggs. Further useful are mixtures of several such phospholipids such as the trade products

Phospholipon<sup>(R)</sup> 100 (95% natural phosphatidylcholine from soybeans)

Phospholipon<sup>(R)</sup> 100 H (98% fully hydrogenated phosphatidylcholine from soybeans) Phospholipon<sup>(R)</sup> 80 (phospholipids from soybeans comprising 76% of phosphatidylcholine and 12% of phosphatidylethanolamine).

Synthetic phosphatides are for instance:

dihexadecanoylphosphatidylcholine,  
ditetradecanoylphosphatidylcholine,  
dioleoylphosphatidylcholine,  
dilinoylphosphatidylcholine,  
in particular

dipalmitoylphosphatidylcholine and  
dipalmitoylphosphatidylglycerol.

Auxiliary agents are for instance cholesterol, derivatives of bile acids and salts thereof, benzylalcohol, neutral oils (Miglyol 812) and glycerol.

5 The production of the preparations according to the present invention is further illustrated in the following examples.

Example 1	
Ebselen	0.110 g
DPPC (dipalmitoylphosphatidylcholine)	13.330 g
DPPG (dipalmitoylphosphatidylglycerol)	1.330 g
cholesterol	6.450 g
buffering agent to pH4	up to 1000 ml

Ebselen, DPPC, DPPG and cholesterol are dissolved in a mixture of 1 part of methanol and 1 part of chloroform. The solvent is removed and the resulting film is hydrated with buffer under an inert gas. Glas balls are added and liposomes are formed with stirring. They are filtered in usual manner under sterile conditions and filled into ampoules.

Example 2	
Ebselen	0.150 g
DPPC	18.180 g
DPPG	1.818 g
cholesterol	8.790 g
water for injections	up to 1000 ml

The products are mixed and further processed as described in example 1.

Example 3	
Ebselen	0.250 g
DPPC	30.300 g
DPPG	3.030 g
cholesterol	14.650 g
buffering agent	up to 1000 ml

The products are mixed and further processed as described in example 1.

Example 4	
Ebselen	0.330 g
DPPC	39.970 g
DPPG	3.997 g
cholesterol	19.338 g
buffering agent	up to 1000 ml

The products are mixed and further processed as described in example 1.

Example 5	
Ebselen	0.400 g
DPPC	48.480 g
DPPG	4.848 g
cholesterol	23.440 g
buffering agent	up to 1000 ml

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The products are mixed and further processed as described in in example 1.

Example 6	
Ebselen	0.430 g
DPPC	50.170 g
DPPG	5.017 g
cholesterol	24.112 g
buffering agent	up to 1000 ml

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The products are mixed and further processed as described in in example 1.

Example 7	
Ebselen	0.100 g
Phospholipon <sup>(R)</sup> 100	45.215 g
sodiumdesoxycholate	17.621 g
benzylalcohol	15.700 g
water for injections	up to 1000 ml

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Ebselen and Phospholipon 100 are dissolved in ethanol. After removal of the solvent under vacuum, the resulting mixture is stirred into a solution of sodiumdesoxycholate. After the addition of benzylalcohol and water as described in example 1, the solution is filtered under sterile conditions and filled into ampoules.

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Example 8	
Ebselen	0.300 g
Phospholipon <sup>(R)</sup> 100	116.900 g
sodiumdesoxycholate	45.900 g
benzylalcohol	15.700 g
water for injections	up to 1000 ml

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The products are mixed and further processed as described in in example 7.

Example 9	
Ebselen	0.300 g
Phospholipon <sup>(R)</sup> 100	116.900 g
glycocholin acid	58.200 g
NaOH	5.000 g
benzylalcohol	15.700 g
water for injections	up to 1000 ml

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Example 10	
Ebselen	0.300 g
Phospholipon <sup>(R)</sup> 80	116.900 g
imrocholin acid	64.370 g
NaOH	5.000 g
benzylalcohol	15.700 g
water for injections	up to 1000 ml

The products are mixed and further processed as described in in example 7.

Example 11	
Ebselen	0.450 g
Phospholipon <sup>(R)</sup> 100	110.440 g
sodium cholate	40.125 g
benzylalcohol	15.700 g
water for injections	up to 1000 ml

The products are mixed and further processed as described in in example 7.

Example 12	
Ebselen	0.500 g
Phospholipon <sup>(R)</sup> 80	108.700 g
water for injections	up to 1000 ml

Ebselen and Phospholipon <sup>(R)</sup> 100 are dispersed with stirring in water for injection purposes. The resulting mixture is treated in the high pressure homogenator. The further subsequent filtration under sterile conditions and filling into ampoules is executed as described in example 1.

Example 13	
Ebselen	0.420 g
Phospholipon <sup>(R)</sup> 80	111.250 g
water for injections	up to 1000 ml

The products are mixed and further processed as described in in example 12.

Example 14	
Ebselen	0.200 g
lecithine	20.000 g
Miglyol 812	170.000 g
glycerol	16.000 g
water for injections	up to 1000 ml

Ebselen is dissolved in Miglyol 812 and lecithine (solution I). Glycerol is added to the water for injection purposes (solution II). Both solutions are mixed and treated in the high pressure homogenator. The resulting emulsion is sterilised in the autoclave and filled into ampoules as usual.

Example 15	
Ebselen	0.500 g
lecithine	24.000 g
Miglyol 812	200.000 g
glycerol	32.000 g
water for injections	up to 1000 ml

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The products are mixed and further processed as described in in example 14.

Example 16	
Ebselen	1.000 g
lecithine	24.000 g
Miglyol 812	200.000 g
glycerol	32.000 g
water for injections	up to 1000 ml

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The products are mixed and further processed as described in in example 14.

Example 17	
Ebselen	2.000 g
lecithine	32.000 g
Miglyol 812	220.000 g
glycerol	37.000 g
water for injections	up to 1000 ml

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The products are mixed and further processed as described in in example 14.

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#### Claims

1. Stable parenteral solutions of 2-phenyl-1.2-benzisoselenazol-3(2H)-one, characterized in that they contain a water-soluble combination of 2-phenyl-1.2-benzisoselenazol-3(2H)-one with one or several phospholipids.

2. Solution according to claim 1, characterized in that the weight proportion of 2-phenyl-1.2-benzisoselenazol-3(2H)-one and the phospholipid or phospholipids in the solution is between 1:2500 to 1:15.

3. Solution according to claim 1 or 2, characterized in that the phospholipid or the phospholipids represent natural or synthetic phospholipids.

4. Solution according to claims 1 to 3, characterized in that it comprises as natural phospholipid the compound soybean lecithine or egg lecithine or a highly purified fraction thereof.

5. Solution according to claims 1 to 3, characterized in that the synthetic phospholipid is phosphatidyl choline, phosphatidyl glycerol or a mixture thereof.

6. Process for producing drug preparations as claimed in claims 1 to 5, characterized in that 2-phenyl-1.2-benzisoselenazol-3(2H)-one (Ebselen) is mixed with the phospholipid or a mixture of several phospholipids and, possibly, one or several additional auxiliary agents in known manner, the mixture is added to a physiological saline solution, the resulting physiological solution is rendered neutral, possibly by means of additional auxiliary agents, and the resulting solution is rendered sterile.

7. The use of solutions according to any of claims 1 to 5 comprising a combination of 2-phenyl-1.2-benzisoselenazol-3(2H)-one (Ebselen) and one or several phospholipids and, possibly, one or several auxiliary agents, for the preparation of drugs.